REMARKS

Claims 1-20, 22-26, 29-55 and 57-58 remain pending upon entry of the present amendment. The Examiner requests Applicants to indicate in the response to this Office Action any other applications so related. Applicants assume the Examiner is referring to patent filings other than the ones the Examiner has already cited. Other related commonly owned patent filings are US 5,604,102, US 5,850,003, US 6,245,964, USSN 09/838,556, US 5,877,015, USSN 08/464,250, and USSN 09/520,581. The last three of these filings were previously assigned to a third party but are now assigned to Elan Pharmaceuticals (the successor in interest to Athena Neurosciences).

The Examiner acknowledges that claims 8, 10, 12, 14, 35, 37, 39 and 41 are free of the prior art. The Examiner acknowledges that the prior art did not teach or suggest a method for testing compounds for an effect on an Alzheimer's disease using a transgenic mouse and testing the markers claimed.

Obviousness type Double Patenting Rejection

The Examiner continues to provisionally reject claims 1-20, 22-26 and 28-58 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7, 9-16 and 18-27 of copending Application No. 09/149,856. Applicant will consider filing a terminal disclaimer once allowable subject matter has been indicated.

The Examiner continues to reject claims 1-20, 22, 23, 26, 29-50, 53, 54, 57 and 58 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 5,811,633. Specifically, the claims are drawn to a method of assay using a mouse. It is submitted that this rejection is moot in view of the amendment to claim 1 and claim 33 excluding transgenes with a region encoding an Aβ-containing protein consisting of a combination of APP cDNA encoding exons 1-6 and 9-18 and genomic APP sequences encoding introns 6, 7 and 8, and exons 7 and 8.

The Examiner continues to reject claims 1-20, 22, 23, 36, 29-50, 53, 54, 57 and 58 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 5,720,936. . It is submitted that this rejection is moot in view of the amendment to claims 1 and 33 discussed above.

The Examiner continues to reject claims 1, 2, 5-20, 24-26, 28-30, 33-48, 51-53 and 56-58 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 5,612,486. It is submitted that this rejection

raises essentially the same issues as the prior art rejection over the same patent discussed below. Applicants respond in the same manner.

The Examiner.continues to reject claims 1, 2, 5-20, 24-26, 28-30, 33-48, 51-53 and 56-58 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 6 and 10-12 of U.S. Patent No. 5,604,102. It is submitted that this rejection raises essentially the same issues as the prior art rejection over the same patent discussed below. Applicants respond in the same manner.

Same invention double patenting

Claims 1-20, 22, 23, 26, 29-50, 53, 54, 57 and 58 stand rejected as directed to an invention not patentably distinct from claims 1-6 of commonly assigned US 5,811,633 and 5,720,936. It is submitted that this rejection is moot in view of the amendment to claim 1 and claim 33 as discussed above.

Showing under 37 CFR 1.78(c) and 35 U.S.C. 132

The Examiner says that commonly assigned U.S. Patent 5,811,633 and U.S. Patent 5,720,936 would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. The Examiner requires that the assignee show under 37 CFR 1.78(c) and 35 U.S.C. 132 that the conflicting inventions were commonly owned at the time the invention was made or to name the prior inventor of the conflicting subject matter. It is submitted that this rejection is moot in view of the amendment to claims 1 and 33 discussed in connection with the double patenting rejections.

Rejection under 35 U.S.C. 102(a)

The Examiner rejects claims 1, 2, 5-7, 9, 11, 13, 15-20, 24-26, 28-30, 33, 34, 36, 38, 40 and 42-48, 51-53 and 56-58 under 35 U.S.C. 102(a) as being anticipated by WO 95/11968. According to the Examiner, the reference teaches a method for identifying drugs effective in treating Alzheimer's Disease wherein the assay comprises administering drugs to transgenic mammals that express the Swedish mutation APP operatively linked to the rat NSE promoter (citing page 39-40, bridge parag.; page 41, lines 16-22 and page 42, lines 17-24). The Examiner contends that as the construct disclosed in the reference is also claimed by applicant and that the

expression levels, characteristics and features claimed for the mouse of the presently-claimed assay are an inherent feature of the mouse of the assay in the '968 patent. The Examiner maintains that the claims of WO 95/11968 meet the structural requirement of the instant claims and the phenotype would be expected to be the same. According to the Examiner, the ordinary artisan would have expected a transgenic mouse of identical structure to achieve the phenotype, and recognizing such a phenotype after publication of WO 95/11968 does not lend patentability. Further, the Examiner says that Applicant has not established that the rate of mice not achieving the claimed phenotype would be so inconsistent that inherency would have been precluded.

In response, Applicants reiterate that an artisan attempting to produce transgenic animals in accordance with the teachings of WO 95/11968 would not necessarily have obtained a transgenic animal having the expression levels of Aβ peptide recited in the present claims. As the Examiner is no doubt aware, the expression levels resulting from any particular transgene may depend not only on the nature of the transgene itself, but also on unpredictable f actors, such as the chromosomal location at which the transgene integrates and the number of copies of the transgene that integrate per genome. Therefore, although transgenic animals produced in accordance with the cited reference may have a transgene that falls within the present claims, they do not necessarily have other structural requirements (e.g., appropriate chromosomal location and copy number) to achieve the expression levels of Aβ peptide recited in the present claims.

Whether the artisan would have in fact achieved a transgenic animal having the expression levels of Aβ peptide recited in the present claims depends on a number of variables. These variable include the number of animals that the artisan would have been prepared to screen, the criteria which the artisan used in screening, and the probability that a given transgenic animal produced in accordance with the teachings of the cited reference would have the recited expression levels of Aβ peptide. The number of animals the artisan would be prepared to screen is a subjective factor depending on the artisan. The criteria the artisan would use for screening would again depend on the artisan. For example, the artisan might screen for expression levels of APP alone rather than Aβ peptide. Alternatively, the artisan might simply screen for some pathological indicia of Alzheimer's disease. An artisan screening by a different criterion would not necessarily obtain a transgenic animal with the recited expression levels of Aβ peptide. Finally, the cited application provides no indication of the frequency with which the a transgene described in the application might integrate so as to give rise to the expression levels of Aβ peptide recited in the present claims, if at all. In these circumstances, it is submitted that whether the artisan would have achieved a transgenic animal having the expression levels of Aβ peptide

recited in the present claims would have been a matter depending on subjective factors, probabilities and unknowns.

Applicant submits that the doctrine of inherency cannot be invoked to find the instant claims unpatentable in these circumstances. Respectfully, two conditions ***must*** be met before the doctrine of inherency may be invoked to find an invention unpatentable. The two conditions are as follows:

1. The feature deemed inherent must always and invariably occur in the prior art.

The law is clear that the allegedly inherent feature must always and invariably occur in the prior art. The question of inherency is not resolved by what an ordinary artisan would expect. *See Mehl/Biophile v. Milgraum,* 192 F.3d 1362, 1365, 52 U.S.P.Q.2d 1303, 1305 (Fed. Cir. 1999) ("Inherency ... ***may not be established by probabilities or possibilities***"); *In re Rijckaert*, 9 F.3d 1531, 28 U.S.P.Q.2d 1955 (Fed. Cir. 1993) ("The mere fact that a certain thing ***may*** result from a given set of circumstances ***is not sufficient*** to establish inherency."). Thus, to show that a phenotype or an expression level is inherent in animals transformed with a construct, the Examiner is required to show that those animals containing the construct will always and invariably have the allegedly inherent phenotype or produce at the allegedly inherent production levels. *See Gubelmann v. Gang*, 408 F.2d 758, 766, 161 U.S.P.Q. 216, 222 (C.C.P.A. 1969) ("it is not sufficient that a person following the disclosure might obtain the result set forth in the count; ***it must invariably happen***."); *In re Oelrich*, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981) ("when the reference is silent about the asserted inherent characteristic...[extrinsic] evidence must make clear that the missing descriptive matter is ***necessarily present*** in the thing described...").

2. Those of ordinary skill in the art must recognize and appreciate the feature deemed inherent in the prior art.

The law is also clear that those of ordinary skill in the art must recognize and appreciate the allegedly inherent feature. *See In re Oelrich*, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981) ("when the reference is silent about the asserted inherent characteristic...[extrinsic] evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, ***and that it would be so recognized by persons of ordinary skill***"); *Glaxo v. Novopharm*, 52 F.3d 1043, 1047, 34 USPQ2d 1565, 1567

(Fed. Cir. 1995) ("for anticipation, the description need not be express, but may anticipate by inherency ***where it would be appreciated by one of ordinary skill in the art***").

Here, whether an artisan would achieve a transgenic animal having the expression levels of Aβ recited in the present claims depends on probabilities, unknowns, and subjective factors, such as how many animals the artisan would screen and what criteria the artisan would use to screen them. The evidence that the Examiner offers is insufficient to support the very high standard required for inherency as established by the above case law. The Examiner has not shown that the expression levels of Aβ recited in the present claims would necessarily occur in a transgenic animal resulting following the teachings of the cited art, or that those of ordinary skill in the art would recognize and appreciate that such had occurred.

Rejection under 35 U.S.C. 102(b)

The Examiner rejects claims 1-7, 9, 11, 13, 15-20, 22, 23, 26, 29-34, 36, 38, 40, 42-50, 53, 54, 57 and 58 under 35 U.S.C. 102(b) as being anticipated by WO 93/14200. According to the Examiner, the reference teaches a method of screening for compounds effective in the treatment of Alzheimer's Diseases using transgenic mice that express a transgene encoding APP770, APP751, APP695, APP770 with FAD mutations at amino acid 717 operably linked to the PDGFβ promoter (citing page 14, parag. 1, page 15, parag. 1, page 16, parag. 1, pages 18, parag. 1, lines 4-5 and pages 28-30). Allegedly, the construct disclosed in the reference is the same as that claimed by applicant, and as such the expression levels, characteristics and features of the mouse of the presently claimed assay are an inherent feature of the mouse testing model of the reference. It is submitted that this rejection is moot in view of the amendment to claims 1 and 33 discussed in connection with the same invention double patenting.

Rejection under 35 U.S.C. 102(e)

1. U.S. Patent No. 5,720,936

The Examiner rejects claims 1, 7, 9, 11, 13, 15-20, 22-23, 26, 28-34, 36, 38, 40, 42-50 and 53-58 under 35 U.S.C. 102(e) as anticipated by U.S. Patent No. 5,720,936. According to the Examiner, the patent teaches an assay system comprising transgenic mice whose genome comprises and expresses a variety of APP transgene constructs: cDNA encoding APP770, APP751, APP695 and FAD mutants of these cDNAs and a cDNA genomic construct, a specific

version of which is claimed (citing col. 8, 13-22, lines 46 to col. 9, line 23; and claims 1-6). The construct is operatively linked to a promoter such as the PDGF promoter (citing col. 9, lines 60-64 and claims 1, 3 and 4). Those mice would allegedly inherently develop the features instantly claimed. The Examiner notes that the only claims that exclude the cDNA/genomic DNA APP construct are claims 28 and 56. However, as discussed above applicants have now amended claims 1 and 33 to include the elements from claims 28 and 56 respectively. Accordingly, it is submitted that the rejection is moot.

2. U.S. Patent No. 5,604,102

The Examiner rejects claims 1, 2, 5-7, 9, 11, 13, 15-20, 24-26, 28, 29, 33, 34, 36, 37, 39, 40, 42-45, 51-53 and 56-58 under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 5,604,102. According to the Examiner, the'102 patent teaches a method of assay employing a transgenic mouse whose genome comprises a transgene comprising APP695 K595M, N596L, the Swedish mutation operably linked to the NSE promoter (citing col. 15, lines 26-31 and col. 20, lines 16-20, and claims 1-16). These mutations are allegedly identical to K670M, N671L. The variation in numbering is allegedly due to the '102 patent referring to the APP695 numbering and the instant claims to the APP770 numbering. The content of the '102 patent is similar to that of the WO 95/11968 cited under 102(a) and raises the same issues. Applicants respond as above.

Rejection under 35 U.S.C. 102(f)

1. U.S. Patent No. 5,720,936

The Examiner rejects claims 1-7, 9, 11, 13, 15-20, 22, 23, 26, 28-34, 36, 38, 40, 42-50 and 53-58 under 35 U.S.C. 102(f) because Applicant allegedly did not invent the claimed subject matter. According to the Examiner, the '936 patent teaches an assay system comprising transgenic mice whose genome comprises and expresses a variety of APP transgene constructs: cDNA encoding APP770, APP751, APP695 and FAD mutants of these cDNAs and a cDNA genomic construct, a specific version of which is claimed (citing col. 8, 13-22, lines 46 to col. 9, line 23; and claims 1-6). The construct is disclosed and claimed to be operatively linked to a promoter such as the PDGF promoter (citing col. 9, lines 60-64 and claims 1, 3 and 4). The '936 patent is presently commonly assigned to Athena Neurosciences. The record indicates that at the time of invention the '936 patent was assigned to TSI Corporation. It is submitted that the

citation of the '936 patent under 35 USC 102(f) raises the same issues as under 102(e). Applicants respond as above.

2. U.S. Patent No. 5,604,102

The Examiner rejects claims 1, 2, 5-7, 9, 11, 13, 15-20, 24-26, 29, 33, 34, 36, 38, 40, 42-45, 51-53 and 56-58 under 35 U.S.C. 102(f) because Applicant allegedly did not invent the claimed subject matter. The '102 patent teaches a method of assay employing a transgenic mouse whose genome comprises a transgene comprising APP695 K595M, N596L, the Swedish mutation operably linked to the NSE promoter (citing col. 15, lines 26-31 and col. 20, lines 16-20, and claims 1-16). The Examiner contends that these mutations are identical to K670M, N671L. The variation in numbering is allegedly due to the '102 patent referring to the APP695 numbering and the instant claims to the APP770 numbering. It is submitted that citation of the above patent under 35 USC 102(f) raises the same issues as under 102(e) and applicants respond as above.

Rejection under 35 U.S.C. 103

1. Games et al., Nature, 373:523-527 (1995)

The Examiner rejects claims 1-20, 22, 23, 26, 29-50, 53, 54, 57 and 58 under 35 U.S.C. 103(a) as being unpatentable over Games *et al.*, *Nature*, 373:523-527 (1995). Games *et al.* allegedly teach, and thereby offer motivation, that the transgenic mice disclosed therein can be used to determine the effectiveness of compounds that lower Aβ production *in vitro* in an *in vivo* assay (citing page 527, col. 1, parag. 1, lines 8-13). The transgenic mice of Games *et al.* express a transgene encoding APP770 V717F operatively linked to the PDGFβ promoter and to develop brain morphologies associated with Alzheimer's Disease: dense plaques, GFAP, neuritic processes, synaptophysin and MAP-2 (citing page 524, col. 2, parag. 1, lines 10-12 and page 526, col. 1, lines 19-21; col. 1-2, bridg, sent. and col. 2, lines 11-14). As explained, *supra*, regarding the rejection under 35 U.S.C. 102(b) of WO 93/14200, Applicant herein excludes the transgene discussed by Games *et al.* as the Examiner requests.

2. U.S. Patent No. 5,811,633

The Examiner rejects claims 1-7, 9, 11, 13, 15-20, 22, 23, 26, 29-34, 36, 38, 40, 42-50, 53, 54, 57 and 58 under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,811,633. According to the Examiner, the '633 patent teaches transgenic mice whose genome comprises and expresses a variety of APP transgene constructs: cDNA encoding APP770,

APP751, APP695 and FAD mutants of these cDNA's and a cDNA genomic construct, a specific version of which is claimed (citing col. 7, line 65 to col. 8, line 8, line 32 to col. 9, line 8 and claims 1 and 3-6). The construct is disclosed and claimed to be operatively linked to a promoter, and such as the PDGF promoter (citing col. 9, lines 43-48 and claims 1 and 6). The mice are allegedly taught to be an assay model for determining compounds for the treatment of Alzheimer's Disease (col. 15, lines 31-40). As discussed in connection with Games above, applicants have excluded the transgene of the exemplary mouse in the '633 patent. Accordingly, it is submitted that the rejection is moot.

3. U.S. Patent No. 5,612,486

The Examiner rejects claims 1, 2, 5-7, 9, 11, 13, 15-20, 24-26, 28-30, 33, 34, 36, 38, 40, 42-48, 51-53 and 56 under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,612,486. According to the Examiner, the'486 patent teaches a transgenic mouse whose genome comprises a transgene comprising APP695 K595M, N596L, the Swedish mutation operably linked to the NSE promoter (citing col. 13, line 56-66; col. 24, lines 45-53 and col. 20, lines 16-20, and claims 1-16). These mutations are allegedly identical to K670M, N671L. The variation in numbering is allegedly due to '486 referring to the APP695 numbering and the instant claims to the APP770 numbering. APP695 K670M, N671L is specifically claimed. The mice of '486 are taught to be useful in screening assays to determine pharmaceuticals for treating Alzheimer's Disease (citing col. 23, lines 44-50). The specification allegedly defines the NSE promoter as one promoter to be used in the instant claims.

In response, it is noted that the teaching of the '486 patent for producing transgenic mice is essentially the same as WO 95/11968 discussed above. As discussed in connection with the '968 application, whether an artisan would in fact achieve a transgenic mouse from the teachings of the '986 application (or by implication the '486 patent) would depend on subjective factors, probabilities and unknowns. The additional issue raised under 103 is whether the teaching of the '486 patent can be combined with teaching of a secondary reference or common knowledge in the art such that the presently claimed transgenic animals, although not inherent from the teaching of the '486 patent, might nevertheless be obvious from it in combination with the secondary reference or common knowledge. However, the Examiner has not identified a secondary reference or common knowledge in the art to apply in combination with the '486 patent. In these circumstances, it is submitted that the present claims would not

have been obvious from the '486 patent for at least the same reasons that they are not anticipated by it.

Rejection under 35 U.S.C. 112

The Examiner rejects claims 1-20, 22-26 and 28-58 under 35 U.S.C. 112, first paragraph, as allegedly being enabled only for methods for testing or screening compounds for an effect on an Alzheimer's disease marker wherein a compound of interest is administered to transgenic mice as exemplified by the present application. The Examiner says that the claims are too broad in view of prior failures of others to produce transgenic mice with indicia of Alzheimer's disease and the unpredictable nature of the art. The Examiner also notes particular difficulties in making transgenic animals with the recited expression levels using wildtype transgenes. The Examiner says that behavioral markers and brain morphological markers cannot be used in cell assays. The Examiner says that insufficient evidence has been provided regarding whether markers recited in claims 8, 10, 12, 14, 35, 37, 39 and 41 are correlated with Alzheimer's disease.

As an initial matter, Applicants note that the claims have been amended so that they no longer refer to wildtype transgenes. Thus, the Examiner's specific concerns with such transgenes are moot.

More generally, Applicants have acknowledged in connection with certain of the art rejections that there is lack of certainty whether an artisan following the teachings of the cited art would necessarily have obtained a transgenic animal with the expression levels of Aβ peptide recited in the present claims. Nevertheless, Applicants submit that there is a crucial distinction as to the relevance of the lack of certainty for consideration of obviousness/anticipation versus enablement. That is, enablement is determined from the combination of the teachings of the present specification and the prior art, whereas obviousness/anticipation is determined from the prior art alone. Whereas the artisan attempting to follow the teaching of the prior art might be uncertain as to how many transgenic animals he should screen, and what he should screen them for, an artisan having the benefit of read the present specification, begins his screening with the knowledge that transgenic animals having the expression levels of Aβ peptide recited in the claims can be achieved, and that these expression levels of Aβ peptide provide an appropriate criterion for screening. Fortified with such knowledge, the artisan is more likely to persist in

screening a sufficient number of transgenic animals until he isolates one having the expression levels of Aβ specified in the present claims.

The first paragraph of section 112 requires that a patent application be written so as to "enable any person skilled in the art to which it pertains...to make and use the same". Applicant through detailed objective guidance and examples teaches the manner and process of making and using the invention in terms commensurate in scope with the claims. "Under these circumstances, the specification is presumptively sufficient; it must be taken as... [enabling] unless there is reason to doubt the objective truth of the statements contained therein which must be relied upon for enabling support". *In re Marzocchi & Horton*, 169 U.S.P.Q. 367,369 (C.C.P.A. 1971) (emphasis in original); M.P.E.P. §706.03. It is well recognized that meeting one stated objective is sufficient to satisfy the "how to use" requirement of Section 112.

A specification "may be enabling even though some experimentation is necessary", *United States v. Telectronics, Inc.*, 857 F.2d 778, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988) so long as the amount of experimentation required is not "undue experimentation". *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). The standard is whether or not the specification "provides a ***reasonable amount of guidance*** with respect to the direction in which the experimentation should proceed". *Id.* Further, no working examples are required in a specification in order for it to meet the requirements of §112, first paragraph.. *In re Borkowski et al.*, 422 F.2d 904, 164 USPQ 642 (C.C.P.A. 1970).

The Federal Circuit considered what constitutes "undue experimentation" in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). In *Wands*, the Board of Patent Appeals and Interferences had rejected a claimed immunoassay method for the detection of Hepatitis B virus using high-affinity monoclonal antibodies to a viral surface antigen (IgM anti-HBsAg antibodies) as not enabled under §112, first paragraph. Evidence showed that over a two year period some 140 hybridomas within the scope of the claims were produced, about 12 were tested, and about 5 of the 12 had the claimed affinity. The Federal Circuit articulated that ***a success rate of only 2.8%*** (representing 4 out of 143 hybridomas) ***would not necessarily have precluded legal enablement.*** The Federal Circuit found that "practitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody" (858 F.2d at 740).

The Examiner says that the facts of *Wands* are not analogous to the present case in view of the unpredictable nature of screening for transgenic animals, and in particular the failure of others to generate transgenic animals with indicia of Alzheimer's pathology. However, applicants submit that in fact the antibody and transgenic animal fields are subject to similar unpredictabilities. In the antibody art, upredictability arises due to the large numbers of

permutations with which antibody genes can rearrange in genomic DNA and also due to somatic mutations in rearranged genes. Empirical screening is required to isolate a B cell that has undergone the appropriate rearrangement and somatic mutation to produce an antibody with desired characteristics. In general, when one attempts to isolate an antibody de novo, it is unpredictable how many antibodies from a given repertoire one would have to screen to isolate the desired antibody. Similarly, in the transgenic field, unpredictability arises from the fact that random factors can influence the site(s) of integration and number of copies of a transgene within a genome, and both of these factors in turn influence subsequent expression levels. As in the antibody art, de novo isolation isolation of a transgenic animal with a desired property is an empirical and uncertain process. However, once feasibility is established generating further transgenic animals with the same desired property is largely a matter of persistence in performing the same routine screening sufficient times until success is achieved. Under Wands, repetition of routine screening very many times does not constitute undue experimentation.

The Examiner says that the Lannfelt reference indicates that previous workers have failed in generating transgenic animals with characteristics of Alzheimer's disease due to difficulty in obtaining a high level of expression of the APP transgene. In fact, however, Lannfelt *et al.* only notes that expression level of the APP transgene were low in the failed animals. Lannfelt does not say that achieving a high level of expression of the APP transgene would have been difficult if this had been one's goal. Moreover, the present claims also specify levels of expression Aβ peptide, which levels are not discussed by Lannfelt.

The Examiner also points out that behavioral markers of Alzheimer's disease would be applicable only to screening methods on transgenic animals per se, and not to cells derived from such methods. Applicants agree. However, such would be as apparent to the skilled person as to the Examiner. "It is always possible to theorize some combination of circumstances which would render a claimed composition or method inoperative, but the art-skilled would assuredly not choose such a combination." Ex parte Janin, 209 USPQ 761 (PTOBIA 1979). "Claims need not recite...factors where one of ordinary skill...would consider them obvious." In re Skrivan, 166 USPQ 85 (CCPA 1970).

The Examiner also points to certain screening markers recited in claim 8 as not having been correlated with Alzheimer's disease. In response, it is noted that the specification discloses that the recited markers are proteins whose expression level, activity or histology is known or suspected to be altered by Alzheimer's disease (see specification at pp. 51-59). As such, the markers would be useful to a researcher in indicating that an agent under test exhibited an activity that was different in kind or degree in transgenic animals with Alzheimer's disease

characteristics than in control animals. Although such an experiment may not necessarily indicate that an agent is effective in treating Alzheimer's disease, the experiment does indicate that the agent exerts a pharmacological activity that differs between transgenic animals with Alzheimer's pathology and control transgenic animals. Given that many test agents are likely to show either no activity at all or no differential activity between transgenic animals and control animals, screens using such markers are valuable in identifying a subset of compounds exhibiting a pharmacological activity worthy of further testing. The subset of compounds can then be tested for causative activity in treating Alzheimer's disease in other assays. In these circumstances, it is submitted that the the skilled person can use the markers specified in claim 8 for screening libraries of compounds for a pharmacological activity without undue experimentation.

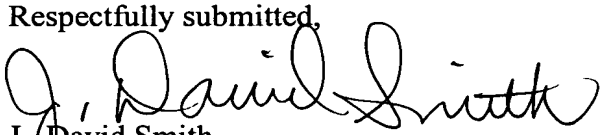
For all of these reasons, applicants request that the lack of enablement rejection be withdrawn.

CONCLUSION

In view of the foregoing, Applicant believes all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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MARKED UP COPY OF THE CLAIMS AMENDED

1. A method for testing compounds for an effect on an Alzheimer's disease marker comprising

a) administering the compound to be tested to a transgenic mouse, or cells derived from the transgenic mouse, wherein the transgenic mouse has a nucleic acid construct stably incorporated into the genome, wherein the construct comprises a promoter for expression of the construct in a mammalian cell and a region encoding an Aβ-containing protein, wherein the promoter is operatively linked to the region,

wherein the region comprises DNA encoding the Aβ-containing protein, wherein the Aβ-containing protein consists of all or a contiguous portion of a protein selected from the group consisting of

[APP770,] APP770 bearing a mutation in one or more of the amino acids selected from the group consisting of amino acid 669, 670, 671, 690, 692, and 717, [APP751,] APP751 bearing a mutation in one or more of the amino acids selected from the group consisting of amino acid 669, 670, 671, 690, 692, and 717, [APP695, and] APP695 bearing a mutation in one or more of the amino acids selected from the group consisting of amino acid 669, 670, 671, 690, 692, and 717,

wherein the Aβ-containing protein includes amino acids 672 to 714 of human APP,

<u>wherein the region encoding an Aβ-containing protein does not consist of a combination of APP cDNA encoding exons 1-6 and 9-18 and genomic APP sequences encoding introns 6, 7 and 8, and exons 7 and 8,</u>

wherein the promoter mediates expression of the construct such that Aβtot is expressed at a level of at least 30 nanograms per gram of brain tissue of the mouse when it is two to four months old, Aβ1-42 is expressed at a level of at least 8.5 nanograms per gram of brain tissue of the mouse when it is two to four months old, APP and APP combined are expressed at a level of at least 150 picomoles per gram of brain tissue of the mouse when it is two to four months old, APPβ is expressed at a level of at least 40 picomoles per gram of brain tissue of the mouse when it is two to four months old, and[/or mRNA] encoding the Aβ-containing protein is expressed to a level at least twice that of mRNA encoding the endogenous APP of the transgenic mouse in brain tissue of the mouse when it is two to four months old;

wherein the transgenic mouse develops plaques that stain with Congo red; and

detecting or measuring the Alzheimer's disease marker such that any difference between the marker in the transgenic mouse, or by cells derived from the transgenic mouse, and the marker in

a transgenic mouse to which the compound has not been administered, or by cells derived from the transgenic mouse to which the compound has not been administered, is observed,
wherein an observed difference in the marker indicates that the compound has an effect on the marker.

33. A method for screening compounds for an effect on an Alzheimer's disease marker comprising

a) administering the compound to be tested to a transgenic mouse, or cells derived from the transgenic mouse, wherein the transgenic mouse has a nucleic acid construct stably incorporated into the genome, wherein the construct comprises a promoter for expression of the construct in a mammalian cell operatively linked to a region of the construct encoding a human amyloid precursor protein,
wherein the region of the construct encoding a human amyloid precursor protein is selected from the group consisting of [APP770 cDNA;] APP770 cDNA bearing a mutation in the codon encoding amino acid 669, 670, 671, 690, 692, 717, or a combination of these mutations; [APP751 cDNA;] APP751 cDNA bearing a mutation in the codon encoding amino acid 669, 670, 671, 690, 692, 717, or a combination of these mutations; [APP695 cDNA; the] APP695 cDNA bearing a mutation in the codon encoding amino acid 669, 670, 671, 690, 692, 717, or a combination of these mutations; APP695, APP751, or APP770 cDNA truncated at amino acid 671 or 685; APP cDNA truncated to encode amino acids 646 to 770 of APP; a combination cDNA/genomic APP gene construct; a combination cDNA/genomic APP gene construct bearing a mutation in the codon encoding amino acid 669, 670, 671, 690, 692, 717, or a combination of these mutations; and a combination cDNA/genomic APP gene construct truncated at amino acid 671 or 685;
wherein the region encoding a human amyloid precursor protein does not consist of a combination of APP cDNA encoding exons 1-6 and 9-18 and genomic APP sequences encoding introns 6, 7 and 8, and exons 7 and 8
wherein Aβ is expressed at a level of at least 50 ng/g brain tissue in the transgenic mouse when the transgenic mouse is three months of age;
wherein the transgenic mouse develops plaques that stain with Congo red; and
detecting or measuring the Alzheimer's disease marker such that any difference between the marker in the transgenic mouse, or by cells derived from the transgenic mouse, and the marker in a transgenic mouse to which the compound has not been administered, or by cells derived from the transgenic mouse to which the compound has not been administered, is observed,

wherein an observed difference in the marker indicates that the compound has an effect on the marker.